

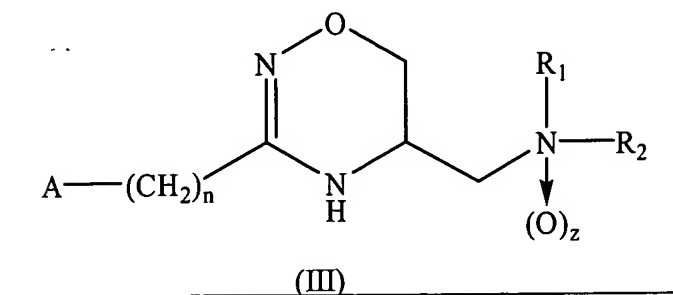
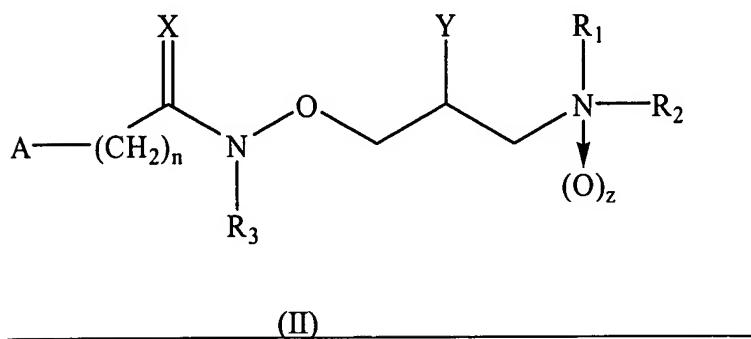
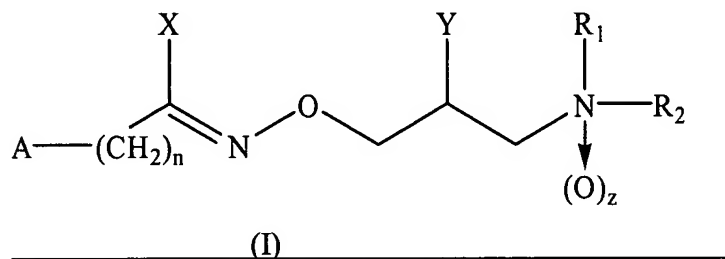
In the Specification

Please insert the following new paragraph after the Title of the invention on page 1, line 4:

This application is the U.S. national stage application of International patent application No. PCT/HU03/00003, filed January 10, 2003.

Please substitute the following paragraph on page 1, beginning at line 7 through to page 2, line 30:

The invention relates to the use of compounds of general formulae (I), (II) and (III) —



R<sup>1</sup> and R<sup>2</sup> independently represent a hydrogen atom or a straight or branched C<sub>1-6</sub> alkyl group optionally substituted with a phenyl group, or

R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom attached thereto form a 5-7 membered saturated heterocyclic ring optionally containing further nitrogen and/or oxygen heteroatoms, which heterocyclic ring is optionally substituted with one or more hydroxy, oxo or benzyl groups,

A represents a phenyl group optionally substituted with one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl or nitro groups or halogen atoms, or a 5-6 membered heteroaromatic ring containing one or more nitrogen, oxygen or sulfur heteroatoms, optionally having N-oxide structure on the nitrogen heteroatom,

n is zero, 1 or 2,

n is zero or 1,

in compounds of general formulae (I), X represents a halogen atom or —NR<sup>4</sup>R<sup>5</sup> group, where R<sup>4</sup> and R<sup>5</sup> independently represent a hydrogen atom or a straight or branched C<sub>1-6</sub> alkyl group,

in compounds of general formulae (II), X refers to oxygen atom,

R<sup>3</sup> represents a hydrogen atom or a straight or branched C<sub>1-6</sub> alkyl group, Y represents a hydrogen atom or hydroxy group, halogen atom or C<sub>1-22</sub> acyloxy group, with the restriction that if R<sup>4</sup> and R<sup>5</sup> are simultaneously hydrogen atoms, Y is other than hydroxy group,

with the proviso that in compounds of general formulae ~~formulae~~ formulae (I) and (II) where Y is other than halogen,

a) R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom attached thereto form a 5-7 membered, saturated heterocyclic ring optionally containing further nitrogen and/or oxygen heteroatom, which heterocyclic ring is substituted with one or more hydroxy, oxo or benzyl groups and/or

b) A ~~is a~~ is an N-containing heteroaromatic ring, which has N-oxide structure on the nitrogen heteroatom, and/or

c) z is 1,

with the further proviso that if X is halo and Y is hydroxy or acyloxy in compounds of general formulae (I),

R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom attached thereto form a 5-7 membered, saturated heterocyclic ring optionally containing further nitrogen and/or oxygen heteroatom, which heterocyclic ring is substituted with one or more hydroxy, oxo or benzyl groups and

with the proviso for compounds of general formulae (III) that if  $R^1$  and  $R^2$  independently represent a hydrogen atom or a straight or branched  $C_{1-6}$  alkyl group optionally substituted with a phenyl group, or together with the nitrogen atom attached thereto form a 5-7 membered saturated heterocyclic ring optionally containing further nitrogen and/or oxygen heteroatoms, then A is a heteroaromatic ring containing oxygen or sulfur heteroatom or an N-containing heteroaromatic ring having N-oxide structure on the nitrogen heteroatom and if A is a phenyl group optionally substituted with one or more  $C_{1-4}$  alkyl,  $C_{1-4}$  haloalkyl or nitro groups or halogen atoms, or a 5-6 membered N-containing heteroaromatic ring, then  $R^1$  and  $R^2$  together with the nitrogen atom attached thereto form a 5-7 membered, saturated heterocyclic ring optionally containing further nitrogen and/or oxygen heteroatom, which heterocyclic ring is substituted with one or more hydroxy, oxo or benzyl groups, and of the salts and optically active forms of the above compounds for the production of pharmaceutical products used in the treatment and/or prevention of vascular diseases or diseases related to vascular disorders.

Please substitute the following paragraph on page 3, beginning at line 11:

We have found that when the hydroxylamine derivatives described in the cited literature are chemically modified, preferably in such a way that, according to general ~~formulae~~ formulae (I), (II) and (III) above,

Please substitute the following paragraph on page 3, beginning at line 27 through to page 4, line 2:

Based on this observation, this invention relates to the use of compounds of general ~~formulae~~ formulae (I), (II) and (III) — where  $R^1$ ,  $R^2$ ,  $R^3$ , A, X, Y, n and z are as above -, and to the use of the salts and optically active forms of the above compounds for the production of pharmaceutical products for the treatment and/or prevention of vascular diseases or diseases associated with vascular disorders.

Please substitute the following paragraphs on page 4, beginning at line 3 through to page 5, line 8:

A considerable part of compounds of general ~~formulae~~ formulae (I), (II) and (III) are novel compounds.

Novel compounds are compounds of general ~~formulae~~ formulae (I) wherein R<sup>1</sup> and R<sup>2</sup> independently represent a hydrogen atom or a straight or branched C<sub>1-6</sub> alkyl group optionally substituted with a phenyl group, or

R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom attached thereto form a 5-7 membered saturated heterocyclic ring optionally containing further nitrogen and/or oxygen heteroatoms, which heterocyclic ring is optionally substituted with one or more hydroxy, oxo or benzyl groups,

A represents a phenyl group optionally substituted with one or more C<sub>1-4</sub> alkyl, C<sub>1-4</sub> haloalkyl or nitro groups or halogen atoms, or a 5-6 membered heteroaromatic ring containing one or more nitrogen, oxygen or sulfur heteroatoms, optionally having N-oxide structure on the nitrogen heteroatom,

n is zero, 1 or 2,

z is zero or 1,

X represents a halogen atom or —NR<sup>4</sup>R<sup>5</sup> group, where R<sup>4</sup> and R<sup>5</sup> independently represent a hydrogen atom or a straight or branched C<sub>1-6</sub> alkyl group,

Y represents a hydrogen atom or hydroxy group, halogen atom or C<sub>1-22</sub> acyloxy group, with the restriction that if R<sup>4</sup> and R<sup>5</sup> are simultaneously hydrogen atoms, then Y is other than hydroxy group, with the proviso that

a) if Y is hydrogen and/or X is a —NR<sup>4</sup>R<sup>5</sup> group, where R<sup>4</sup> and R<sup>5</sup> have the above meanings,

R<sup>1</sup> and R<sup>2</sup> together with the nitrogen atom attached thereto form a 5-7 membered, saturated heterocyclic ring optionally containing further nitrogen and/or oxygen heteroatom, which heterocyclic ring is substituted with one or more hydroxy, oxo or benzyl groups and/or

A is a N-containing heteroaromatic ring, which has N-oxide structure on the nitrogen heteroatom, or

b) if X is halo and Y is hydroxy or acyloxy,

$R^1$  and  $R^2$  together with the nitrogen atom attached thereto form a 5-7 5 membered, saturated heterocyclic ring optionally containing further nitrogen and/or oxygen heteroatom, which heterocyclic ring is substituted with one or more hydroxy, oxo or benzyl groups, and the stereoisomers of the above compounds and their salts.

Please substitute the following paragraph on page 7, beginning at line 2:

The invention relates to the above compounds. The invention further relates to pharmaceutical products that contain as active ingredient compounds of general ~~formulae~~ formulae (I), (II) and (III), or their stereoisomers, or their salts, where  $R^1$ ,  $R^2$ ,  $R^3$ , A, X, Y, n and z are as defined above.

Please substitute the following Table 2 beginning on page 9, line 25, through to page 10, line

29:

Table 2. The vessel relaxing effect of the compounds of the invention on the thoracic aorta of SH rats (in vitro testing).			
Materials	Ach doses (M)		
Doses	$10^{-6}$	$10^{-5}$	$10^{-4}$
SH control N = 10	55.1	57.2	72.0
Reference n=12; 20 mg/kg	77.4	80.2	81.7
Compound no. 4 n=11; 5 mg/kg	82.5	84.9	88.1
Compound no. 8 n=11; 20 mg/kg	80.3	88.0	89.2
Compound no. 9 n=10; 5 mg/kg	87.0	87.9	93.2
Compound no. 11 n=12; 10 mg/kg	79.7	85.1	86.0
Compound no. 12 n=12; 20 mg/kg	82.3	83.5	80.4
Compound no. 13 n=10	88.4	90.3	95.2

Please substitute the following text in Table 3 on page 11, at line 27:

SH control, physiological ~~saline~~ saline solution

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Please substitute the following Examples 14-19 beginning on page 22, line 14, through to page 24, line 25:

**Example 14.****Tablets**

(+)-5,6-dihydro-5-[(1-piperidinyl)-methyl-3-(3-pyridyl)--4H-1,2,4-oxadiazine	20.0 mg
corn starch	100.0 mg
lactose	95.0 mg
talc	4.5 mg
magnesium stearate	0.5 mg

The active compound is finely ground, mixed with the excipients, the mixture 25 is homogenized and granulated. The granulate is pressed into tablets.

**Example 15.****Capsules**

5,6-dihydro-5-[(1-piperidinyl)-methyl-3-(3-pyridyl)--4H-1,2,4-oxadiazine	20.0 mg
microcrystalline cellulose	99.0 mg
amorphous silica	1.0 mg

The active ingredient is mixed with the additives, the mixture is homogenized and filled into gelatine capsules.

**Example 16.****Dragées**

N-[3-(1-oxido-1-piperidinyl)propoxy]-3-nitro-benzimidoyl-chloride dihydrate	25.0 mg
lactose	82.5 mg
potato starch	33.0 mg
polyvinyl pyrrolidone	4.0 mg
magnesium stearate	0.5 mg

The active ingredient and the polyvinyl pyrrolidone are dissolved in ethanol. The lactose and the potato starch are mixed, and the mixture is evenly wetted with the granulating solution of the active ingredient. After sieving, the wet granulate is dried at 50 °C and sieved. Magnesium stearate is added and the granulate is pressed into dragée cores, which are then coated with sugar and polished with bee wax.

**Example 17.****Suppositories**

5,6-dihydro-5-[(4-benzyl-1-piperidinyl)-methyl]-3-(3-pyridyl)-4H-1,2,4-oxadiazine	4.0 mg
cocoa butter	3.5 g
solid fat 50 suppository mass	15.0 g

The cocoa butter and the suppository mass are heated to 40 °C, the active ingredient is dispersed in the melt, then the mass is cast into suppository forms.

**Example 18.****Solution**

5,6-dihydro-5-[(4-hydroxy-1-piperidinyl)methyl]-3-(3-pyridyl)-4H-1,2,4-oxadiazine hydrochloride	500 mg
sorbite	10 g
saccharin sodium	0.05 g
twice distilled water	q. s. ad 100 ml

**Example 19.****Injection**

N-[2-chloro-3-(1-piperidinyl)propoxy]-3-benzimidoyl-chloride hydrochloride	2 mg
physiological saline solution, pyrogen-free, sterile	q. s. ad 2.0 ml

The solution is filled into 2 ml vials and the vials are sealed.



After page 32: Please insert as new page 33 the attached Abstract of the Disclosure.